Specialty Conference

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Symposium on Adolescent Gynecology and Endocrinology

Part II: Secondary Amenorrhea, Hirsutism in Adolescents and the Clinical Consequences of Stilbestrol Exposure *In Utero*

Secondary Amenorrhea

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SECONDARY AMENORRHEA is commonly defined as the absence of menses for six months in a patient who has previously had regular menses, or the absence for 12 months in a patient with previous irregular menses. Before the differential diagnosis in these patients is considered, thyroid disease, diabetes mellitus, and normal or abnormal pregnancies should be ruled out with determinations of thyroid-stimulating hormone (TSH), triiodothyronine (T_3) and thyroxine (T_4); some assessment of thyroxin-binding globulin (by a T_3 resin uptake or immunoassay of the globulin); a fasting blood glucose determination, and a pregnancy test, preferably by the beta human chorionic gonadotropin radioimmunoassay method. If these tests give normal findings the patients may be divided into the following three categories: (1) patients with no evidence of galactorrhea, cortisol or androgen excess, (2) patients with galactorrhea or (3) those with possible cortisol excess (Cushing syndrome) or androgen excess (or both). Patients with androgen excess will be discussed in a separate section of this symposium. Only patients with amenorrhea with or without galactorrhea are discussed in this section.

Amenorrheic Patients Without Galactorrhea

Patients with amenorrhea and no clinical evidence of excess cortisol (Cushing syndrome) or androgen production or galactorrhea can first be divided into two groups based upon whether or not they have uterine bleeding following the intramuscular injection of 100 or 200 mg of progesterone-in-oil. The positive or negative response of the endometrium to progesterone has been shown to correlate with levels of serum estradiol.[37] For the test results to be considered positive, the amount of uterine bleeding can be minimal dark

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
DES = diethylstilbestrol
DHEA = dehydroepiandrosterone
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
HMG = human menopausal gonadotropin
LH = luteinizing hormone
PCO = polycystic ovarian (disease)
PRL = prolactin
T_3 = triiodothyronine
T_4 = thyroxine
TeBG = testosterone-estradiol-binding globulin (sex steriod binding globulin)
TSH = thyroid-stimulating hormone

brown staining or a normal menstrual flow. When uterine bleeding takes place, it usually occurs between 3 and 14 days after the intramuscular injection. Amenorrhea in patients with normal breast development and an intact uterus may be due to hypothalamic-pituitary-ovarian dysfunction or uterine disease.

Hypothalamic Causes

- *Hypothalamic dysfunction*

One of the most common causes of amenorrhea is anovulation secondary to hypothalamic dysfunction without any history of stress or drug intake. The dysfunction may be due to failure of estradiol to rise sufficiently enough to trigger the luteinizing hormone (LH) surge. The primary defect may be a neurotransmitter derangement. In patients with this disorder levels of estradiol are at least 40 pg per ml and, therefore, uterine bleeding occurs following progesterone administration.[37] The serum follicle-stimulating hormone (FSH) and LH levels are in the normal range in these patients.

- *Hypothalamic dysfunction secondary to medications*

The drugs most commonly associated with amenorrhea are the phenothiazine derivatives and the contraceptive steroids. The action of the tranquilizers appears to be due to catecholamine depletion. Recent data have shown that contraceptive steroids have a suppressive effect on the pituitary in addition to their inhibitory effect on the hypothalamus.[38] In most of the patients with amenorrhea due to drugs there are normal serum FSH, LH and estradiol levels and, therefore, there will be uterine bleeding following progesterone administration.

- *Hypothalamic dysfunction secondary to stress*

In some patients amenorrhea will develop when a stress situation is encountered (for example, going away to school or divorce in the family). In these patients there most often are normal levels of FSH, LH and estradiol, and, therefore, uterine bleeding occurs following progesterone administration.

- *Hypothalamic failure secondary to either lesions of the hypothalamus or lack of GnRH synthesis*

These disorders are rare and may present as either primary or secondary amenorrhea. Lesions of the hypothalamus which have been associated with amenorrhea include craniopharyngioma, tuberculous granuloma and the sequelae of meningoencephalitis. In most patients with such disorders no demonstrable lesion can be found. The amenorrhea is most likely due to the lack of gonadotropin-releasing hormone (GnRH).[39] In these patients estradiol levels are low and uterine bleeding will not occur after progesterone administration. Randomly determined serum FSH and LH levels are either very low or in the low normal range, and are insufficient to stimulate the ovarian follicles to synthesize estradiol.

- *Hypothalamic amenorrhea secondary to weight loss*

This group includes patients with simple weight loss and anorexia nervosa.[40] Patients with simple weight loss are those who become amenorrheic after losing 15 percent to 20 percent of ideal body weight (usually referred to as being underweight) or those with greater than 25 percent weight loss who are considered to be severely underweight. In these persons there may be normal or low gonadotropin and estrogen levels depending on the degree of weight loss. Patients with anorexia nervosa in addition to having severe weight loss (greater than 25 percent of ideal body weight) have the added complaints of constipation, hypotension, bradycardia and hypothermia. These persons invariably have an abnormal ideation concerning their body image and have an aversion to food intake. They have low serum gonadotropin and estrogen levels. In addition, almost every patient with anorexia nervosa, in contrast to those with simple weight loss, has low serum T_3 and normal serum T_4 levels.

Treatment in these two groups of patients ap-

pears to be primarily related to regaining body weight. Patients with anorexia nervosa need psychiatric therapy.

Pituitary Causes of Amenorrhea

Patients with amenorrhea due to a pituitary abnormality may have nonneoplastic lesions or tumors.[37]

- *Nonneoplastic lesions of the pituitary*

This group includes patients with a destructive process of the pituitary such as that seen in the Sheehan syndrome due to postpartum hemorrhage. The pituitary cells are damaged either by anoxia, thrombosis or hemorrhage. These patients have low serum levels of LH, FSH and estradiol and, therefore, will not bleed following intramuscular injection of progesterone. Depending on the extent of the pituitary destruction, many of these patients also have hypothyroidism and adrenal insufficiency. These patients must have a total pituitary evaluation using insulin-induced hypoglycemia to evaluate their growth hormone, prolactin and adrenocorticotropic hormone (ACTH), which is measured indirectly by serum cortisol response. These patients may need thyroxin and glucocortocoid replacement therapy.

- *Pituitary tumors*

Amenorrhea may be the first sign of a pituitary tumor. Chromophobe adenomas are the most common pituitary tumor reported in association with amenorrhea. These tumors do not secrete hormones and should be considered as different tumors than prolactin-secreting adenomas which are associated with galactorrhea. Galactorrheic patients presenting with or without menstrual disorders are considered below.

Patients with amenorrhea secondary to pituitary tumors usually have low serum estrogen levels and, therefore, do not have uterine bleeding following intramuscular administration of progesterone. A random determination of serum levels of FSH and LH may give findings either low or normal. Therefore, polytomographic studies of the sella turcica must be obtained in all amenorrheic patients who do not have withdrawal bleeding and have either low or normal levels of serum FSH. If the patient is found to have a tumor, surgical operation or radiation (or both) is usually indicated. Use of replacement hormone therapy will be dependent on the functional status of the pituitary following therapy.

Ovarian Causes of Amenorrhea

There are four ovarian causes of amenorrhea listed in this section. Three of these disorders result in ovarian failure and include premature ovarian failure, loss of ovarian function secondary to castration, infection, hemorrhage or compromised blood supply, and autoimmune oophoritis. The fourth ovarian cause is polycystic ovarian (PCO) disease. Some investigators have stated that PCO disease is due to hypothalamic disorder, but the reason for including it under ovarian causes of amenorrhea is the morphological changes found in the ovaries of patients with the disease.

- *Premature ovarian failure*

This diagnosis is made when ovarian failure occurs at any age between the onset of menarche and age 35. Because the ovaries do not secrete sufficient amounts of estradiol to maintain the negative feedback on the hypothalamus in these patients, the gonadotropins are found to be elevated into the postmenopausal range. Although gonadotropin levels do fluctuate, the levels are consistently elevated and, therefore, a single serum FSH determination is adequate to make the diagnosis. Such patients will not have uterine bleeding following intramuscular administration of progesterone.[37,41] With rare exceptions ovulation cannot be induced with drug therapy and, therefore, these patients should be considered sterile and considered to require estrogen replacement.

- *Loss of the ovarian function secondary to castration, intraovarian infection or interference of blood supply*

Loss of ovarian function following surgical castration is self-explanatory. On rare occasions, patients with severe bilateral tubo-ovarian abscesses have responded well to antibiotic therapy and do not require surgical treatment. In some of these patients the infection completely destroys the ovarian tissue resulting in ovarian failure. Compromise of the ovarian blood supply following hysterectomy may result in cystic degeneration. Usually this process is unilateral and, therefore, amenorrhea does not occur. However, it may occur bilaterally or in the only remaining ovary resulting in loss of ovarian function. These patients are sterile and need estrogen replacement.

- *Autoimmune oophoritis*

Autoimmune endocrine disorders, particularly Hashimoto thyroiditis, are common. These auto-

immune endocrinopathies may affect a single organ or may involve multiple organs. Because in a patient who presents with autoimmune destruction of an endocrine organ, failure of the other glands may develop over the ensuing years, physicians should be continuously observant for the appearance of additional endocrinopathies. The glands affected in the approximate order of occurrence are thyroid, beta cells of the pancreas, adrenals, ovaries, parathyroids, and testes. Ovulation may still occur in a patient with oophoritis if oligomenorrhea is present. Once amenorrhea appears, these patients are infertile and estrogen deficient and should be treated with estrogen replacement therapy.

- *Polycystic ovarian disease*

Patients with PCO disease usually have oligomenorrhea but many have primary or secondary amenorrhea. These patients secrete normal amounts of estradiol and, therefore, have uterine bleeding following intramuscular progesterone administration. It has been reported that 60 percent to 80 percent of patients with PCO disease have elevated serum LH values above 20 mIU per ml and a low normal level of serum FSH. The elevated LH value has been used to differentiate this disorder from patients with hypothalamic dysfunction who have normal levels of serum LH. Although LH does have significant daily fluctuations it has been reported that in patients with PCO disease a single measurement of LH is adequate to make this diagnosis since the fluctuations are usually elevated above the 95 percent confidence limits for normal premenopausal women.

If the patient desires pregnancy, clomiphene citrate is the therapy of choice. If the patient does not desire pregnancy, she should be given cyclic progestin therapy in order to induce uterine bleeding and prevent unopposed estrogen effect on the endometrium which may lead to either benign or atypical hyperplasia. One mode of progestin therapy is to give the patient 10 mg a day of medroxyprogesterone acetate orally for at least five days each month.

Uterine Factors (Uterine Synechiae or the Asherman Syndrome)

Before the above diagnoses can be considered and the appropriate laboratory tests ordered, the uterine factor must be ruled out.[42] The formation of uterine synechiae has usually been associated with dilation and curettage or endometritis. This condition has also been seen following myomectomy and metroplasty and cesarean section. Either total or only partial obliteration of the endometrial cavity may be found. In patients with partial disease, uterine bleeding can be induced with estrogen-progestin therapy. Therefore, this regimen is not always definitive in establishing the diagnosis. Whenever this diagnosis is suggested by history the patient should have an

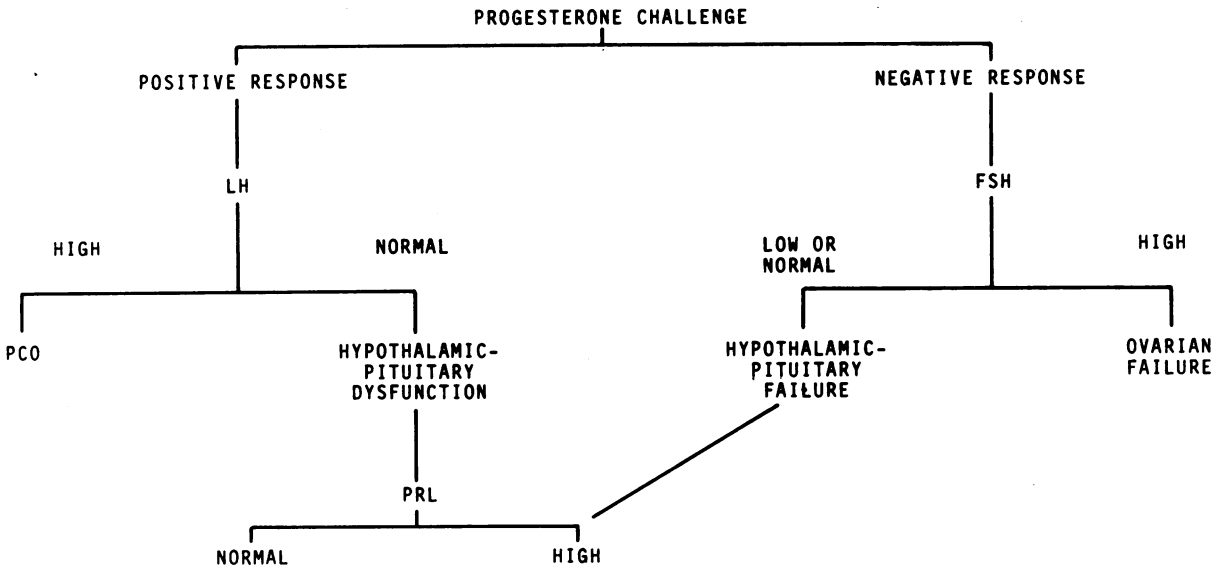

Figure 26.—Scheme for evaluation of patients with secondary amenorrhea without galactorrhea or cortisol or androgen excess. FSH = follicle-stimulating hormone, LH = luteinizing hormone, PCO = polycystic ovarian disease, PRL = prolactin.

evaluation of the uterine cavity by either hysteroscopy or hysterosalpingography. In order to be able to use a simplified approach for the workup of patients with amenorrhea, uterine factors (including pregnancy) must be ruled out.

Evaluation and Therapy

Studies of withdrawal uterine bleeding following an injection of progesterone-in-oil has made it possible to separate cases of amenorrhea into two major categories (Figure 26). In those persons with uterine bleeding a single serum LH value greater than 30 mIU per ml is indicative of polycystic ovarian disease. Normal LH values indicate hypothalamic dysfunction. In these patients a serum prolactin (PRL) determination should be ordered even in the absence of galactorrhea and, if PRL is found to be elevated, polytomographic x-ray studies of the sella turcica should be done to rule out pituitary tumors. If the PRL value is normal, uterine withdrawal bleeding should be induced at least every three months with oral administration of medroxyprogesterone acetate or intramuscular progesterone-in-oil, if the patient does not desire pregnancy. If pregnancy is desired, there should be treatment with clomiphene citrate. As long as patients remain in the dysfunction group it is unnecessary to carry out x-ray studies of the sella turcica, unless they have galactorrhea in addition to the amenorrhea or serum PRL value is elevated. A single serum FSH study (but not an LH determination*) in patients who do not have uterine bleeding can identify two distinct populations. One group will have a low or normal FSH value and the other an elevated value. The group with low or normal FSH levels represents those patients with hypothalamic-pituitary failure while the group with elevated FSH levels represents patients who have ovarian failure.

In all patients with hypothalamic-pituitary failure, a complete pituitary workup should be done to show the presence or absence of a pituitary tumor. This evaluation should include polytomographic evaluation of the sella turcica, visual field examination and computerized axial tomographic (CAT) scans. If no tumor is shown, a PRL determination should be done every six months and x-ray studies of the sella turcica every 24 months. In addition, an insulin-induced hypoglycemia test should be done in all cases to determine the pituitary growth hormone, PRL and ACTH reserve. Because these patients have very low levels of estradiol, they rarely respond to clomiphene citrate. It is recommended that induction of ovulation be first attempted at doses up to 250 mg per day for five days and if they fail to ovulate following this treatment, then therapy with human menopausal gonadotropin (HMG) should be initiated.

Ovarian failure is easily diagnosed because patients with the disorder invariably fail to respond to progesterone challenge and have elevated FSH values. These patients will not respond to any form of ovulatory drug therapy and, therefore, are sterile and should be given estrogen replacement therapy because they do not have adequate endogenous levels of estrogens. The recommended regimen of estrogen replacement is 0.3 or 0.625 mg of conjugated estrogen given on days 1 through 25 of each month. Medroxyprogesterone acetate (Provera), 10 mg administered orally on days 16 through 25, should be given in order to avoid unopposed estrogen effect on the endometrium.

Amenorrheic Patients With Galactorrhea

Galactorrhea can be associated with hypothyroidism, the use of tranquilizers or antihypertensive drugs and prior use of oral contraceptive steroids. Inappropriate lactation has also been reported in patients with Cushing disease, those with acromegaly and those who have had chest trauma. These patients can have normal menstrual cycles or have a hypothalamic-pituitary derangement resulting in oligomenorrhea or amenorrhea. It was hoped that with the development of a sensitive radioimmunoassay for PRL it would be possible to differentiate patients with pituitary tumors from those who have a functional derangement. Unfortunately, this method has not been totally reliable because galactorrheic patients with microadenomas not only can be ovulating but also can have serum PRL levels in the normal range. Therefore, neither the menstrual history nor the PRL level alone can be relied upon to select those patients in whom radiographic evaluation of the sella turcica is required.

The use of tranquilizers poses a significant clinical problem. If a patient can discontinue the use of tranquilizers, the medication should be stopped and a serum PRL level obtained every month until the level drops into the normal range.

*LH is elevated in patients with ovarian failure and low or normal in patients with hypothalamic-pituitary dysfunction. However, values fluctuate widely and a single LH study may not be diagnostic of either catagory.

If in three months after discontinuing the medication, the serum PRL is still elevated, the patient should have a complete evaluation. If the patient cannot function without the use of tranquilizers, and if the level of PRL is above 100 ng per ml, she should be evaluated as outlined below.

A common misconception is that contraceptive steroids taken by mouth may cause galactorrhea. Such contraceptives do not stimulate galactorrhea but in fact may mask the presence of galactorrhea by their suppressive action on the breast. Therefore, if galactorrhea develops in patients taking contraceptive steroids, the medication should be discontinued and the patient evaluated for the presence of a pituitary adenoma. If galactorrhea develops after the use of steroids is discontinued, the complete workup can be delayed for three months. If the galactorrhea is still present at that time a complete evaluation should be started.

In an effort to develop a systematic method for evaluating patients with galactorrhea we recently reported our experience in a series of 149 patients who presented with galactorrhea at our clinic and private service.[43] None were taking tranquilizers or had any clinical evidence of Cushing disease or acromegaly. Galactorrhea was defined as milky or watery breast secretions noted either spontaneously or by expression. The secretion could be unilateral or bilateral. Localized breast disease should be considered in patients with unilateral galactorrhea. Of the 149 patients, three were found to have primary hypothyroidism, an incidence of 2 percent. Because these patients will recover completely following institution of thyroid replacement therapy, a serum TSH determination should be done in a patient with galactorrhea.

If the patient is euthyroid, a serum PRL study should be carried out even if the patient gives a history of having normal menstrual cycles. In six of our series of 32 patients who had normal menses, changes were found on x-ray studies compatible with pituitary microadenomas. All six of these patients did have elevated serum PRL levels. None of the 13 patients who had normal PRL levels were found to have x-ray evidence of

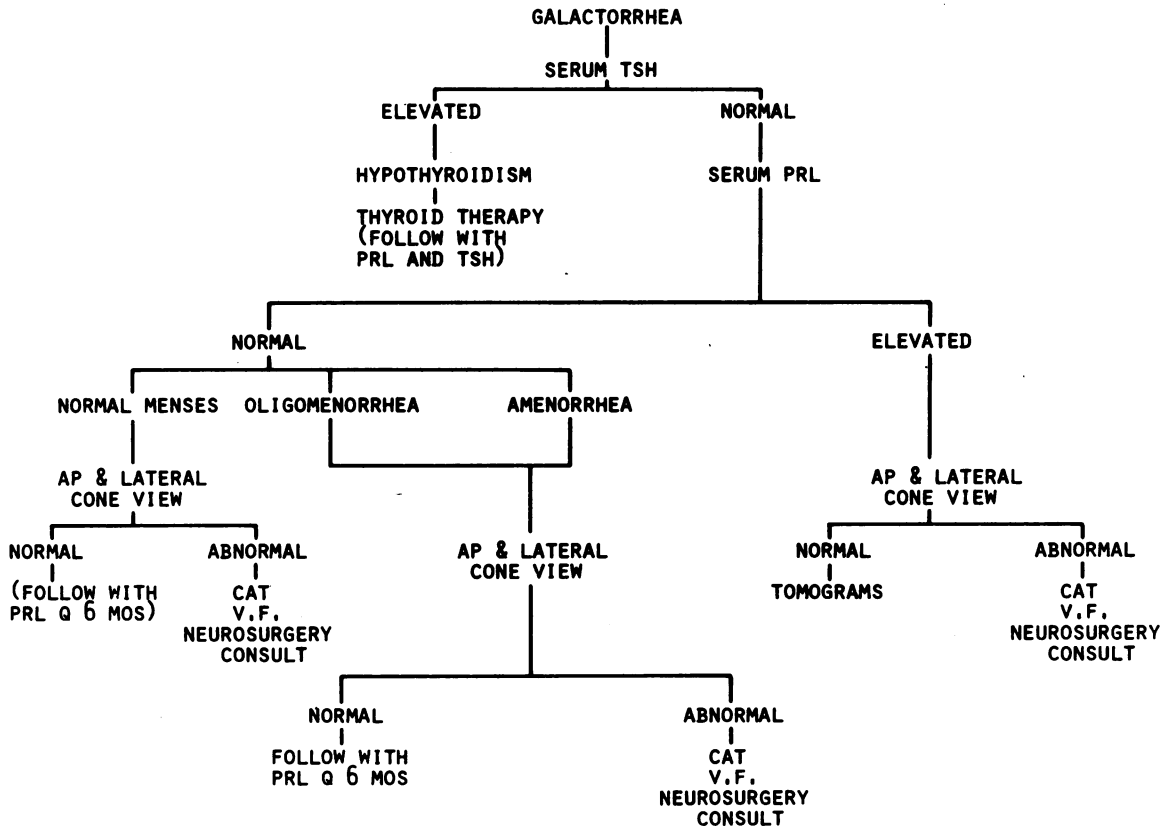

Figure 27.—Schematic outline for the diagnosis and management of patients with galactorrhea. AP = anteroposterior, CAT = computerized axial tomography, PRL = prolactin, TSH = thyroid-stimulating hormone, V.F. = visual field examination.

microadenomas, and, therefore, a low risk category was identified which was comprised of galactorrheic women who were menstruating regularly and had normal PRL levels. In galactorrheic patients who gave a history of either oligomenorrhea or amenorrhea, no such category could be identified because nine patients with normal serum levels of PRL were found to have radiologic evidence compatible with having a pituitary microadenoma. It is clear that galactorrheic patients with amenorrhea, low serum estrogen levels and elevated serum PRL concentrations have a high incidence of pituitary microadenomas. In our series of 42 such patients, 29 (69 percent) had microadenomas.

Utilizing all this information it has been possible to construct an outline for investigating and managing patients with galactorrhea (Figure 27). This approach utilizes a single measurement of serum TSH and PRL in conjunction with the menstrual history and use of polytomograph. The various therapeutic modalities available for treating prolactin-secreting microadenomas or macroadenomas have been discussed recently.[44]

Hirsutism in Adolescents

GLENN D. BRAUNSTEIN, MD*

Normal Hair Growth

HAIR MAY BE CLASSIFIED into three categories: asexual, ambisexual and sexual.[45] Asexual hair, the growth and distribution of which are independent of sex or gonadal steroid production, includes the scalp, eyelash, eyebrow and lumbosacral triangle hair. Ambisexual hair grows in response to low levels of adrenal and gonadal androgens and occurs in both sexes. Thus pubic and axillary hair, hair on limbs and, to a lesser extent, the hair extending along the linea alba from the umbilicus to the pubic triangle fall into this category. Sexual hair is normally restricted to males and is dependent upon the androgen concentration. Beard, moustache, nasal-tip, pinnea, back and chest hair are examples of androgen sensitive sexual hair.[45] Hirsuitism may, therefore, be defined as excessive sexual hair growth in the androgen sensitive areas of the body in a phenotypic female.

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A variety of factors are involved in growth of sexual hair. These include the sensitivity of hair follicles to circulating androgens, the ability of hair follicles to convert weak androgens or androgen precursors to more potent androgens, the potency of the androgens that the hair follicles are exposed to, the location of the hair and the duration of exposure of the follicle to androgens.[46] Sexual hair begins as vellus or fine, lightly pigmented lanugo-type hair which upon exposure to sufficient quantities of androgens may be irreversibly converted to a thick, darkly pigmented, deeply rooted terminal hair. Once a terminal hair is formed it seems that very little androgen is required to maintain hair growth.[47] Terminal sexual hairs go through a growth cycle that varies between two and four years, and at the end of the cycle the hair shaft falls out and new hair formation may take place.[48]

Androgen Metabolism in Women

In a nonpregnant woman, approximately 25 percent of the serum testosterone is derived from direct adrenal secretion, approximately 25 percent from ovarian secretion and 50 percent is derived from peripheral or extraglandular conversion of the 17-ketosteroid androgen precursors, primarily dehydroepiandrosterone (DHEA) (90 percent from adrenal glands, 10 percent from ovaries) and Δ^4-androstenedione (50 percent from adrenal glands, 50 percent from ovaries).[49-51] In addition to testosterone, three other androgens which, like testosterone, are 17β-hydroxysteroids, are important in women. These androgens are Δ^5-androstenediol, dihydrotestosterone and 3 α-androstanediol, and are almost exclusively derived from the extraglandular conversion of DHEA, androstenedione and testosterone.[50] If one takes into account the average plasma concentration of each of these androgens, their relative androgenicity and the amount that exists in the unbound biologically active state in the blood, then an androgenicity index may be computed.[50,52] Therefore, approximately half of the total androgenic activity in the plasma of a normal woman is due to testosterone, while the other three 17β-hydroxysteroids contribute to the remaining androgen activity.

Approximately 99 percent of the circulating androgens are bound to serum proteins, while the remaining 1 percent is unbound and is capable of entering the androgen target tissues to exert its biologic action. The two serum proteins that bind